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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,689	03/25/2004	Mark Larche	3652/2004	7876

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
08/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,689	LARCHE ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,13 and 16-29* is/are pending in the application.

4a) Of the above claim(s) *16-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/18/2008 has been entered.

2. Claims 1-5, 13 and 16-29 are pending.

3. Claims and 16-29 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-5 and 13 are currently under examination as they read on a method of desensitizing a patient to a polypeptide allergen comprising administering to the patient a peptide wherein restriction to DR4 possessed by the patient can be demonstrated for the peptide and the peptide is able to induce a late phase response in an individual who possesses DR4.

5. In view of the amendment filed on 04/18/2008, only the following rejections are maintained.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5 and 13 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants are not enabled for a method of desensitizing a human patient to a **polypeptide allergen** the method comprising administering to the patient **a peptide derived from the allergen** wherein restriction to a MHC Class II molecule possessed by the patient can be demonstrated for the peptide, wherein in the method the peptide induces a late phase response in the patient, and wherein the **peptide has a length of 5 to 50 amino acids** and is not a Fel d I-derived peptide of claim 1; wherein **the peptide** is included in a composition containing **a plurality of peptides derived** from the **said allergen** of claim 2; wherein the **plurality of peptides derived** from said allergen includes **peptides** for which restriction to Class II DR molecules DR2, DR3, DR4 and DR7 can be demonstrated, provided that such **peptides** can be derived from **the allergen** of claim 3; wherein the patient possesses any one of the MHC Class II DR molecules DR2, DR3, DR4 or DR7 of claim 4; wherein the patient possesses the MHC Class II molecule DR4 of claim 5; and a method according to claim 1 wherein the **polypeptide**

allergen is any one of Der p I, Der p II, Der fI or Der fII and **allergens present in any of the following: grass, tree and weed (including ragweed) pollens; fungi and moulds; foods, stinging insects, the chirnomidae (non-biting midges); spiders and mites, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae, bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle, mammals such as cat, dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil** of claim 13 for the same reasons as set forth in the Office Action mailed on 11/19/2007.

Applicant's arguments filed on 04/18/2008 have been fully considered, but are not found persuasive.

Applicants argue that

> "The Examiner has maintained the enablement objection and in particular refers to Francis *et aL,* (2005) Current Opinion in Allergy and Clinical Immunology 5, 537-543. The Examiner has focused on sections of this paper which allegedly refer to potential difficulties in immunotherapy. However it is submitted that these potential difficulties do not fairly reflect the art as a whole, and cannot be used to conclude that the present application is not enabled.
>
> It is well settled that the termination of enablement is based on the evidence as a whole. MPEP §2164.05. If the entirety of Francis *et aL* is considered then it is noted that the authors make very positive comments concerning peptide based tolerisation. In particular, the concluding paragraph shows that the authors consider use of short synthetic peptides as being capable of improving symptoms and improving patients' ability to tolerate allergen exposure, and essentially that peptide therapy is capable of inducing regulatory T cells that can suppress allergen-specific immune responses. Further the paragraph entitled "Purpose of Review" in the abstract of the paper highlights that peptides have the potential to inhibit T cell function but not induce anaphylaxis. Thus we disagree with the Examiner's reading of Francis *et al.,* and instead believe that this paper shows that peptide immunotherapy is effective.
>
> The Examiner has also focused on Kinnunen *et al.* and stats that this document is relevant because use of altered peptide ligands as described in Kinnunen *et aL,* would also be covered by the present claims. However, amended claim 1 requires the peptide to induce a late phase response during the method of desensitization, and thus only covers use of peptides which are effective, i.e. which are capable of being presented by the MHC Class II molecules present in the patient and of stimulating the necessary late phase response. The Examiner has referred to page 7 left hand column, second paragraph of this document which refer to disease exacerbation that was observed in a trial of MS. However, this paragraph also notes that activation of allergen-specific T cells has been shown to precede development of tolerance in

immunotherapy. Therefore Kinnunen *et aL* draws a distinction between therapy of autoimmune disease and therapy of allergy. This distinction is further discussed in the third paragraph of the same column which makes it clear that potential problems with peptide therapy for autoimmune disease are much less likely to occur peptide therapy for allergy. Therefore Kinnunen *et aL* provides no firm reasons to assume that immunotherapy using peptides would not be effective for allergy.

It is submitted that in referring to portions of specific documents to support objections of enablement, the Office Action does not consider the art as a whole and has not given a fair weight to other disclosure in the same documents or in the documents filed with Applicants' previous response that show that peptide immunotherapy is successful in treatment of allergic disease. When teaching across the art is looked at, it can be concluded that use of peptides to tolerise against allergens has been successful.

The Examiner also notes that the specification does not describe use of non- Fel d-I derived peptides to desensitise patients. However it is not necessary for the specification to describe each and every peptide which could be used in the method of claim 1 as long as such peptides could be obtained by the skilled person by routine means available in the art or with the aid of the teaching in the specification. Again, Applicants note that the law is clear that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. MPEP §2164.06. It would be a routine matter for the skilled person to identify suitable peptides that contained MHC Class II epitopes. The specification provides the sequence for numerous examples of allergens that can be used according to the claimed invention. Examples 5 and 6 of the specification show how epitopes can be identified, for example by using binding studies with MHC molecules or by using peptides to stimulate proliferation of T cells. Such techniques would be considered routine in the art, and thus the skilled person would be able to identify suitable peptides for use in the method of claim 1 for any allergen.

In maintaining the rejection, the Office Action acknowledges that one of skill in the art could perform experimentation to identify allergens and peptides with the claimed functional characteristics, but appears to conclude that the enablement requirement is not satisfied because it would be more than routine experimentation to "determine the MHC restriction of every peptide of 5-50 amino acids of any allergen." Again, the quantity of experimentation is not determinative of enablement, particularly when such experimentation is routine and the specification provides, as in this case, ample teachings to guide the experimentation. In addition, the statement in the Office Action that one of skill in the art would have to "determine the MHC restriction of every 5-50 amino acids of any allergen" in order to practice the invention mischaracterizes the enablement analysis. Given the teachings in the specification and the level of skill in the art, the skilled artisan could routinely determine whether a given peptide antigen could be used in accordance with the claimed invention. The enablement requirement does not necessitate the specification to teach how to make and use every possible variant of the claimed invention. See, e.g., Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004). Accordingly, the specification does enable the invention and Applicants request that the rejection be reconsidered and withdrawn."

Further, one of ordinary skill in the art would be required to perform undue experimentation in order to identify any and all peptides and peptide variants that would be MHC Class II restricted as recited with the claimed functional characteristics to practice the claimed invention. It is not routine experimentation to determine the MHC restriction of every peptide of 5-50 amino acids of any known or unknown allergen and to use those peptides to

desensitize individuals, contrary to Applicant's assertion particularly in light of the state of the art of allergen immunotherapy, as evidenced by the art of Francis et al. and Kinnunen et al. (PTO-892, References U & V).

It is the Examiner's position that the portions of the references cited do reflect the art as a whole because the references are relied upon to establish that the state of the art is unpredictable. The cited references teach that any peptide from any allergen cannot be used to desensitize. Contrary to Applicant's assertion the art as a whole does not teach that allergen immunotherapy is predictable. The state of the art is replete with failed desensitization procedures and the inadvertent induction of anaphylactic shock. The mere presence alone of these facts shows unpredictability. Therefore, the Examiner is unpersuaded by Applicant's assertion that immunotherapy is routine. The Examiner acknowledges that the state of the art is hopeful for the future and has seen limited success. However, successful desensitization procedures are not the norm. In addition, as cited previously, timing, dosage and peptide selection criteria all matter.

Francis et al. specifically teaches on page 538 that cat peptide vaccines are unpredictable because they can be significantly associated with adverse events, vaccination is not significant in comparison to placebo, and that of the some peptides immunotherapies that did work, they were only evident at a single time point post therapy. The reference, written by an inventor of the instant application states "In summary, whereas such studies generally reported modest improvements in clinical and surrogate outcome measures, treatment was associated with a high frequency of adverse reactions." In addition, the co-inventor and co-author of this reference, as

one of ordinary skill in the art at best, actually states in the reference that choosing peptides for immunotherapy is difficult, (not routine experimentation) (In particular, 'Further peptide vaccine design' section on page 541). The whole reference teaches though many examples that peptide selection in immunotherapy makes a difference to the outcome. Therefore, Applicant's assertion that the art as a whole teaches the predictability of peptide immunotherapy is unpersuasive as predictability is not associated with adverse reactions and clinical outcome failure.

Applicant's assertion that "amended claim 1 requires the peptide to induce a late phase response during the method of desensitization, and thus only covers use of peptides which are effective, i.e. which are capable of being presented by the MHC Class II molecules present in the patient and of stimulating the necessary late phase response" which would somehow preclude the use of altered peptide ligands is also unpersuasive. Altered peptide ligands are routinely used to stimulate responses to antigens to which the patient has been previously exposed. Altered peptide ligands are used to change the type of response generated from the engagement with TCR. Since altered peptide ligands are encompassed by the instant claim recitations (peptide derived from the allergen) and may also be presented by MHC II molecules in the patient, it stands to reason that responses generated therefrom are unpredictable to generate desensitization. The state of the art shows that the nature of the cell signals induced by APLs is unpredictable.

8. Claims 1-5 and 13 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed,

had possession of the claimed invention for the same reasons as set forth in the Office action mailed on 03/28/2007.

Applicant is in possession of: the peptides of SEQ ID NO: 1, SEQ ID NO:2 and SEQ ID NO:3 for stimulating T cells in vitro.

Applicant is not in possession of: a method of desensitizing a human patient to a **polypeptide allergen** the method comprising administering to the patient **a peptide derived from the allergen** wherein restriction to a MHC Class II molecule possessed by the patient can be demonstrated for the peptide, wherein in the method the peptide induces a late phase response in the patient, and wherein the **peptide has a length of 5 to 50 amino acids** and is not a Fel d I-derived peptide of claim 1; wherein **the peptide** is included in a composition containing **a plurality of peptides derived** from the **said allergen** of claim 2; wherein the **plurality of peptides derived** from said allergen includes **peptides** for which restriction to Class II DR molecules DR2, DR3, DR4 and DR7 can be demonstrated, provided that such **peptides** can be derived from **the allergen** of claim 3; wherein the patient possesses any one of the MHC Class II DR molecules DR2, DR3, DR4 or DR7 of claim 4; wherein the patient possesses the MHC Class II molecule DR4 of claim 5; and a method according to claim 1 wherein the **polypeptide allergen is any one of Der p I, Der p II, Der fI or Der fII** and **allergens present in any of the following: grass, tree and weed (including ragweed) pollens; fungi and moulds; foods, stinging insects, the chirnomidae (non-biting midges); spiders and mites, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae,**

bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle, mammals such as cat, dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil of claim 13 for the same reasons as set forth in the Office Action mailed on 11/19/2007.

Applicant's arguments filed on 04/18/2008 have been fully considered, but are not found persuasive.

Applicants argue that

> "The specification makes it clear that the peptide must have a specific length and must comprise a sequence that demonstrates restriction to a MHC class II molecule; that is, it must be capable of binding to a MHC Class II molecule possessed by the patient. As shown above, the skilled person can ascertain by routine means whether a peptide is capable of binding to a MHC Class II molecule. Thus the specification describes all of the structural requirements that a peptide must have in order to be capable of being used in the method of claim 1. As stated in Applicants' last response, a common desensitization mechanism exists that can be used to tolerise against an allergen that contains a sequence that demonstrates restriction to a MHC class II molecule. Thus, the structure of a peptide allergen that allows it to bind to an MCH class II molecule correlates with the function of tolerising against that allergen.
>
> Accordingly, the specification, in combination with the knowledge and skill in the art provides ample teachings to evidence to one of skill in the art that Applicants were in possession of the full scope of the claimed invention as of the instant filing date. Applicants, therefore, request that the rejection be reconsidered and withdrawn."

It remains the Examiner's position that the specification has not adequately described a correlation between function (desensitization, induces late phase response) and structure responsible for desensitization and induction of late phase response such that one of ordinary skill in the art would have known what peptides encompassed by claims could be generated to have the disclosed functions. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. "Without a correlation between structure and function, the claims do little more than define the claimed invention by

function. That is not sufficient to satisfy the written description requirement." Ex parte Kubin, 83 U.S.P.Q.2d 1410 (BPAI 2007). The specification does not adequately describe the genus of 5 to 50 amino acid peptides derived from any non-Fel d I allergen for use in the claimed method for desensitization and induction of a late phase response.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-5 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/24281 (IDS filed on 04/24/2007, Reference BE) as evidenced by Tovey et al. (PTO-892, Reference U).

WO 94/24281 teaches a method of desensitizing a patient to a Der p I or Der p II dust mite polypeptide allergen the method comprising administering to the patient one or more peptides derived from the allergen, wherein the peptide has a length of 5 to 50 amino acids and is not a Fel d I-derived peptide (In particular, abstract, whole document).

The limitations of "wherein restriction to a MHC Class II molecule possessed by the patient can be demonstrated for the peptide" and "the peptide is able to induce a late phase

response in an individual who possesses the said MHC Class II molecule" of claim 1; "wherein the plurality of peptides derived from said allergen includes peptides for which restriction to Class II DR molecules DR2, DR3, DR4 and DR7 can be demonstrated, provided that such peptides can be derived from the allergen" of claim 3; "wherein the patient possesses any one of the MHC Class II DR molecules DR2, DR3, DR4 or DR7" of claim 4; "wherein the patient possesses the MHC Class II molecule DR4" of claim 5 are inherent as the same peptide is being administered to the same patient population for the same result. Since the office does not have a laboratory to test the reference peptides, it is applicant's burden to show that the reference peptides are not the peptides recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Tovey et al. is being used an evidentiary reference to show that all humans have been previously exposed to dust mite allergens from birth as they are ubiquitous in dust in the environment. (In particular, whole document). Therefore, the generation of a late phase response in the reference patients is inherent.

The reference teachings anticipate the claimed invention.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 8, 2008

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

/Eileen B. O'Hara/

Supervisory Patent Examiner, Art Unit 1644